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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,040	11/15/2000	Paul J. Carter	11669.185USD3	5212

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,040	CARTER, PAUL J.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,39-44 and 49-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *40-42* is/are allowed.

6)☒ Claim(s) *25,39, 43-44 and 49-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-24, 26-38 and 45-48 are cancelled.

Claims 53-65 have been added.

2. Claims 25, 39-44 and 49-65 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Objections/Rejections

Withdrawn Objections

5. The objection to the specification as disclosing the sequence Cysteine followed by two Prolines and another Cysteine as being represented by "CPC" and not CPPC is withdrawn in view of the amendment to the specification filed 9/13/2006.

Rejections Maintained/New Grounds of Rejections

6. The rejection of claims 25, 39, 43-44, 49-52 and now applied to newly added claims 53-65 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing mew matter is maintained. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a composition comprising a monospecific F(ab')2 that comprises a first and second Fab' each comprising a CH1 domain fused to an amino

acid sequence of up to 10 amino acids that comprises a C-terminal amino acid sequence of Cys-Ala-Ala. There is insufficient written support for the limitation of a CH1 fused to an amino acid sequence of up to 10 amino acids that comprise a C-terminal sequence of Cys-Ala-Ala. The as filed specification discloses at pg. 11 that the Cys-X-X sequence where X is preferably Ala is fused to the C-terminus of the CH1 of Fab'. Further, at pg. 20, lines 4-7, the specification discloses that the heavy chain constant domain downstream from CH1 is deleted and the CH1 domain is followed C-terminally by Cys-Ala-Ala. The only disclosure of 10 amino acid residues is found at pg. 11, lines 25-27, where it is disclosed that the hinge may be entirely omitted in favor of one or more cysteine residues or, preferably short (about 1-10 residues) cysteine-containing polypeptide. Thus, the specification as filed only provides adequate written support for a F(ab')2 comprising a first and second Fab' each comprising a CH1 domain fused directly to the amino acid sequence Cys-Ala-Ala. Additionally, the as filed specification discloses at pp. 29-30 that in order to express the Fab' fragment of huMab4D5-8 the CH1 gene segment was extended to encode part of the cysteine-containing antibody hinge region where cysteine followed by two prolines and another cysteine was chosen (interpreted as CPPC). To prevent the formation of an intramolecular disulfide bond between the two cysteine residues of the CPPC sequence construction of a Fab' variant with a single hinge cysteine residue having the C-terminal sequence Cys-Ala-Ala was produced (see pg. 30, lines 23-27). Thus, while the Fab' variant comprising the CH1-Cys-Ala-Ala sequence, which is three amino acids in length and within the genus of a CH1 domain fused to up to 10 amino acids comprising the C-terminal sequence Cys-

Ala-Ala, this does not provide adequate written support for the broader genus of sequences that are up to 10 or about up to 10 amino acids comprising the C-terminal sequence Cys-Ala-Ala as presently claimed because there is insufficient written description for the sequences contained therein. A subgenus is not necessarily described by a genus encompassing it and a species upon which it reads. *In re Smith*, 458 F.2d 1389, 1395; 173 USPQ 679, 683 (CCPA 1972). The Instant claims recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the present claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

Response to Arguments

The response filed 9/13/2006 states that in contrast to the examiner's contention that the only disclosure of a polypeptide of 10 amino acid residues is found at pg. 11, lines 25-27, the specification provides many places describing cysteine containing polypeptides that have up to 10 amino acids. Applicant points to the specification at pg. 6, lines 24-29 which discloses that the cysteine containing polypeptide can be a hinge region sequence variant containing a single free thiol cysteinyl residue. At pg. 7, lines 25-31 of the specification it discloses that a Fab amino acid sequence can be modified

by deleting or substituting all of the hinge region cysteines C-terminal to the first cysteine. Applicant asserts that one of skill in the art would understand that a Fab amino acid sequence with deletions of all of the hinge region cysteine residues C terminal to the first cysteine of the hinge region of at least an IgG1, IgG2 and IgG4 antibody would have about 10 amino acids or less. This has been fully considered but is not found persuasive. The examiner maintains that the only explicit disclosure of the 10 amino acid length as currently claimed is found at pg. 11, lines 25-31 of the as filed specification, where it is disclosed that the hinge may be entirely omitted in favor of one or more cysteine residues or, preferably short (about 1-10 residues) cysteine-containing polypeptide. The general disclosure of hinge region variants that contain a single free thiol cysteinyl residue and the deletion or substitution of all of the hinge region cysteine residues C-terminal to the first cysteine of the hinge would not have led the skilled artisan to a Fab' comprising a CH1 domain fused to an amino acid sequence of up to 10 amino acids and comprising the C-terminal sequence of Cys-Ala-Ala as currently claimed. There is nothing in the generic disclosure as pointed to by applicant that would have led the skilled artisan to a Fab' containing a CH1 domain fused to an amino acid sequence of about 10 amino acids in length as opposed to an amino acid sequence of about 2, 3, 5, 8, 12, 15, 20, 23, or any other length and comprising the C-terminal sequence Cys-Ala-Ala. The broad genus of hinge region variants as pointed to by applicant, which embraces hinge region variants of any length and any "desired antibody class or isotype" (pg. 11, lines 31-32) would not have led one of skill in the art to a hinge region sequence that is up to about 10 amino acids and contains the C-

terminal sequence Cys-Ala-Ala. The fact that some of the disclosed embodiments may fall within the scope of the presently claimed subgenus does not provide sufficient direction or guidance to the currently claimed limitations. Further, the deletion or substitution of all of the hinge region cysteine residues C-terminal to the first cysteine of the hinge would not have led the skilled artisan to a Fab' comprising a CH1 domain fused to an amino acid sequence of up to 10 amino acids that comprise a C-terminal sequence of Cys-Ala-Ala as currently claimed. For example, the deletion or substitution of all of the hinge region cysteine residues C terminal to the first cysteine of the hinge region of at least an IgG1, IgG2 and IgG4 does not produce a hinge region comprising the C-terminal sequence Cys-Ala-Ala as presently claimed (for support, see Fig. 1 of WO 89/01974, cited on PTO-892 mailed 4/20/2005). Again, the as filed specification discloses at pg. 11 that the Cys-X-X sequence where X is preferably Ala is fused to the C-terminus of the CH1 of Fab'. Further, at pg. 20, lines 4-7, the specification discloses that the heavy chain constant domain downstream from CH1 is deleted and the CH1 domain is followed C-terminally by Cys-Ala-Ala. Thus, the disclosure of the C-terminus of the CH1 of Fab' as being fused to the sequence Cys-Ala-Ala, or a single species falling within the presently claimed subgenus, does not provide sufficient guidance and direction to the broader scope of the claims encompassing the CH1 domain of Fab' fused to an amino acid sequence of about 10 amino acids in length and comprising the C-terminal sequence Cys-Ala-Ala. Applicants' reliance on a generic disclosure and possible a single or limited species has not provided sufficient direction and guidance to the "features" currently claimed. It is noted that a generic or sub-generic disclosure

cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

Applicant acknowledges "The specification does indicate that in some embodiments, the CH1 sequence is fused to the sequence Cys-X-X, wherein X is Ala, Arg, Asp, or Pro", however, applicant argues that this language does not require direct fusion and other descriptions in the specification and claims provide evidence that Applicants specification is not limited to direct fusion. Applicant points to original claim 11 which discloses a Fab' comprising a C-terminal amino acid sequence Cys-Ala-Ala and at pg. 30, lines 26-27 of the specification as filed discloses making a Fab' variant with a single hinge cysteine residue having a C-terminal amino acid sequence Cys-Ala-Ala. Applicant again refers to pg. 6 of the specification, which discloses that the polypeptide sequence fused to the CH1 domain may comprise only the cysteinyl residue or can be present in a polypeptide. Applicant refers to the working example in the specification that teaches that the CH1 domain of huMab4D5-8 was extended to encode part of the cysteine containing hinge sequence (pg. 29, lines 30-32). Applicant concludes that one of skill in the art reading the specification would understand that the Fab' variants were made by including at least a portion of the hinge region and including a C-terminal amino acid sequence of CPPC or CAA and applicant asserts that the examiner has improperly imported the word directly into the claims and the specification. This has been fully considered but is not found persuasive. Again, the as

filed disclosure of a Fab' comprising a C-terminal amino acid sequence Cys-Ala-Ala does not provide adequate written support for the broader limitation of a CH1 fused to an amino acid sequence of about 10 amino acids comprising a C-terminal amino acid sequence of Cys-Ala-Ala. Further, applicants' working example in the specification where the sequence cysteine followed by two prolines and another cysteine (CPPC sequence; found in the naturally occurring human IgG1 hinge region) was selected and used to extend the CH1 domain of huMab4D5-8 and the subsequent replacement of this sequence with Cys-Ala-Ala to preclude intrachain disulfide bond formation (i.e., see example at pg. 29, lines 30-35 and pg. 30, lines 17-29), does not provide adequate written support for the broader limitation of a Fab' comprising a CH1 domain fused to an amino acid sequence that is about 10 amino acids in length and comprises the C-terminal sequence Cys-Ala-Ala because there is no description of what additional sequence in addition to the Cys-Ala-Ala is contained therein. Further, the disclosure that the human IgG1 sequence CPPC was selected and used to extend the CH1 domain of Fab' and the subsequent replacement of this sequence with Cys-Ala-Ala to preclude intrachain disulfide bond formation does not convey any other sequence or structure other than Cys-Ala-Ala as being fused to the CH1 domain of Fab'. The as filed disclosure does not clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. With respect to applicants assertion that the examiner is improperly importing the word "directly" into the claims and specification, the specification at pg. 11, lines 32-35 states "In certain preferred embodiments of this invention, the C-terminus of the CH1 of Fab' is fused to the sequence Cys X X.", where

X is preferably Ala, meaning that *the sequence Cys-Ala-Ala* is fused to the C terminus of the CH1 of Fab'. There is no disclosure of additional sequence being fused to the CH1 domain of Fab' and comprising the C-terminal sequence Cys-Ala-Ala.

The examiner acknowledges applicants' remarks regarding the art of Carter et al (Biotechnology, 10:163-167, February 1992, cited on PTO-892 mailed 8/7/2006), co-authored by the inventor of the present application, however, compliance with the first paragraph of 35 U.S.C. 112 for patentability of the present application depends upon the sufficiency of the as filed disclosure of the present application.

With respect to newly added claims 54-65, the claims recite the limitation wherein the antibody fragment is a Fab' in which a heavy chain CH1 domain is fused to one or more cysteines, or a short cysteine-containing polypeptide of about 1-10 residues, and wherein the Fab' comprises a C-terminal amino acid sequence of Cys-Ala-Ala and wherein the short cysteine containing polypeptide comprises a part of a hinge region and wherein the hinge region has all of the hinge region cysteines C-terminal to the first cysteine deleted or substituted. At the top of pg. 7 of the response filed 9/13/2006, applicant points to originally filed claim 11 as well as various parts of the as filed specification for support. This has been fully considered but is not found persuasive. For reasons set forth above, the as filed disclosure does not provide adequate written support for the present claim limitations, which encompass compositions comprising a Fab' in which the CH1 domain is fused to one or more cysteines, or a short cysteine-containing polypeptide of about 1-10 residues, including part of a hinge region wherein the hinge region has all of the hinge region cysteines C-terminal to the first cysteine

deleted or substituted and a C-terminal sequence of Cys-Ala-Ala. Again, the disclosure of the sequence Cys-Ala-Ala fused to the C-terminus of the CH1 of Fab' (e.g., specification at pg. 11, lines 32-35), the disclosure where the heavy chain constant domain downstream from CH1 is deleted and the CH1 domain is followed C-terminally by Cys-Ala-Ala (specification at pg. 20, lines 4-7) and the disclosure of a Fab' comprising the C-terminal sequence Cys-Ala-Ala (e.g., original claim 11) does not provide adequate written support for (i) the fusion of the CH1 domain of Fab' to one or more cysteines and comprising a C-terminal sequence of Cys-Ala-Ala, (ii) the fusion of the CH1 domain of Fab' to a short cysteine-containing polypeptide of about 1-10 residues and comprising a C-terminal sequence of Cys-Ala-Ala, (iii) the fusion of the CH1 domain of Fab' to part of a hinge region and comprising a C-terminal sequence of Cys-Ala-Ala and (iv) the fusion of the CH1 domain of Fab' to part of a hinge region that has all of the hinge region cysteines C-terminal to the first cysteine deleted or substituted and comprising a C-terminal sequence of Cys-Ala-Ala. Again, a generic or sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Newly added claims 54-65 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in newly added claims 54-65, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112.

Applicant is required to provide sufficient written support for the limitations recited in newly added claims 54-65 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

For these reasons and those already of record, the rejection of claims 25, 39, 43-44 and 49-65 under 35 U.S.C. 112, first paragraph, as introducing mew matter is maintained.

New Grounds of Objections

7. The specification at pg. 30, line 22 discloses the term "CPC terminus" which should be corrected as "CPPC terminus" consistent with applicants' amendment to the specification filed 9/13/2006. Applicants' cooperation is requested in reviewing and correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Interview Request

8. The examiner acknowledges applicants request for an interview. In a telephonic conversation with Applicants' representative, Katherine Kowalchyk, on 11/17/2006 the examiner indicated that applicants' response filed 9/13/2006 does not overcome the rejection of claims 25, 39, 43-44, 49-65 under 35 U.S.C. 112, first paragraph, as introducing mew matter, discussed supra (see item no. 6 above). In view of this, Applicant agreed that the interview would not be necessary at this point in time.

Conclusion

9. Claims 40-42 are free of the prior art.

10. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827